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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,078	07/25/2001	William F. Wade	PM	7302

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PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 08/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,078	WADE ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 5/24/04, has been entered.
Claims 1, 9, 11 and 17 have been amended.
Claims 3-4 and 18-30 have been canceled.

Claims 1, 2 and 5-17 are under consideration in the instant application as they read on the elected invention.

Applicant's election of Group III (claims 1, 2, and 5-17) drawn to a method of enhancing a humoral or CD4 Th1 (DTH, cell-mediated) immune response by administering an antibody-antigen conjugate wherein the antibody binds a dendritic cell antigen and tumor or cancer antigens and an breast cancer antigen with traverse has been acknowledged.

Given applicant's admission that the specific class and type of antigen are obvious variants over one another, the species of classes and types of antigens are held obvious in view of one another in the instant application.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's amendment, filed 5/24/04.
The rejections of record can be found in the previous Office Action, mailed 2/26/04.

3. The filing date of claims 1, 2, 5, 8 and 11-15 is deemed to be the filing date of priority application USSN 60/090,849, filed 6/26/98.

It appears that the filing date of the instant claims drawn to "aged or immunocompromised individuals, human subject fifty years or older (claims 6-7), "toxin" (claim 9), "lung, head and neck, uterine and leukemia" cancer or tumor cells antigens (claim 10), "protozoan disease" (claim 16), "leishmaniniasis, listeriiosis, leprosy or tuberculosis infection" (claim 17) is deemed to be the filing date of priority application PCT/US99/12825, filed 6/25/99.

If applicant desires priority prior to 6/25/99 for claims 6, 7, 9, 10 16 and 17; applicant is invited to point out and provide documentary support for the priority of the instant claims.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Applicant's reliance on the disclosure of enhancing or suppressing at least the humoral immune response to a target antigen, wherein the antigen is expressed by a prostate, breast, ovarian, lung, head and neck, uterine or leukemia cell in the priority applications does not support a prostate, breast, ovarian, lung, head and neck uterine cancer or tumor cell. There is insufficient direction and written description in the priority application USSN 60/090,849 for prostate, breast, ovarian, lung, head and neck uterine cancer or tumor cell. The priority disclosure does not appear to provide written support of prostate, breast, ovarian, lung, head and neck and uterine antigens in the context of a cancer or tumor cell. The disclosure of "leukemia cell" does not provide sufficient written support for conveying the cancer or tumor to the listing of certain tissue/organ sources.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The amendment filed 5/24/04, is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention.

The added material which is not supported by the original disclosure is as follows:
"and gp72", which is disclosed in the replaced paragraph bridging pages 10-11, filed 5/24/04.

The specification appears to provide a written description for "IE protein gp72", but does not appear to provide a written description for a distinct and different molecule "and gp72".

Applicant is required to cancel the new matter in the reply to this Office Action.
Alternatively, applicant is invited to provide direction for the written description for "and gp72" in the specification as filed.

6. Claims 1, 2 and 5-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations accurately reflects the relative efficacy enhancing or suppressing the humoral immune response or CD4 Th1 immune response to a target antigen comprising any conjugate comprising a selected antigen and anti-CD40 antibody encompassed by the claimed therapeutic strategy.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Page 11, paragraph 2, of the instant specification discloses that "whether the immune response is enhanced of suppressed is apparently antigen-dependent as, dependent on the particular antigen, system, the inclusion of the anti-CD40 ligand may enhance, have not effect, or elicit an adverse effect on the humoral immune responses to the target antigen. The specification continues to disclose that" "One of skill in the art can ascertain by routine experimentation whether the anti-CD40 ligand enhances or suppresses humoral immune response to a target antigen."

The disclosed Examples do not appear to support synergistically enhancing or suppressing the humoral immune response or CD4 Th1 immune response to a target antigen.

For example, targeting avidin by anti-CD40 mAb did not induce an antibody response to avidin (see Example 3, including page 29, paragraph 1 of the instant specification).

In addition, page 35, paragraph 1 of the instant specification acknowledges that "targeting avidin to CD40 or CD11c expressed on a dendritic cell or macrophage does not ensure an enhanced serologic response".

Further it is noted here that "it is unclear whether the generation of different signals by CD40 or CD11c ligation compared to class II ligation may affect the efficacy of priming".

Page 36, paragraph 1 of the instant specification discloses that: "Future studies should determine what parameters of the targeted surface molecule are significant for enhance serologic responses to targeted antigen. If the mechanism of affect can be determined, protocols that optimize the adjuvant affect of targeted antigens can be used to effectively immunize aged individuals".

Page 36, paragraph 2 of the instant specification further discloses that "if we are to consistently take advantage of the adjuvant or immunosuppressant properties of CD40 ligation, the dynamics of antigen targeting so as to interpose CD40 at the optimal moment or location will need to be determined for the particular antigen system. In this regard, effective manipulation of APC surface molecules in vivo may not be possible".

The specification does not adequately teach how to effectively synergistically enhance or suppress the humoral immune response or CD4 Th1 immune response to a target antigen with a conjugate comprising "any selected antigen" in vivo by administering antibody-antigen conjugates. The specification does not teach how to extrapolate data obtained from limited experimental observations with limited antigens to the development of synergistically enhancement or suppression of immune responses in vivo, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of synergistically enhances humoral immune responses of CD4 Th1 immune response to any antigen by the administration of antibody-antigen conjugates and anti-CD40 antibodies.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective synergistically enhancing humoral immune responses of CD4 Th1 immune responses, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for synergistically enhancing humoral immune responses of CD4 Th1 immune response to any antigen by the administration of antibody-antigen conjugates and anti-CD40 antibodies

7. Claims 1, 2 and 5-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2 and 5-17 are indefinite in the recitation of "thereby synergistically enhancing or suppressing at least the humoral immune response or CD4 Th1 immune response to the target antigen." This phrase is relative in nature which renders the claim indefinite. The phrase is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention

Applicant's amendment filed 5/24/04 (see page 16, paragraph 1), submits that synergistic enhancement means that the combination of an antigen-antibody conjugate and an anti-CD40 antibody in accordance with the method of the present invention act together to have an effect which is greater than the simple sum of their effects when acting alone.

However the specification as filed does not appear to set forth this definition.

Further, as pointed out above in the rejection under 35 USC 112, first paragraph; it appears that the instant disclosure as well as the Examples are not consistent with synergistically enhancing or suppressing the humroal immune response or CD4 Th1 immune response to a target antigen.

Applicant is invited to provide direction and written support in the specification as filed or objective evidence to support applicant's assertions concerning the metes and bounds of the claimed "limitation".

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

8. Claims 1, 2 and 5-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Anand et al. (US 6,291,208 B1) and Heath (US 2002/0135722 A1) and further in view of applicant's admission that species of classes and types of antigens are held obvious in view of one another in the instant application.

Applicant's arguments, filed 5/24/04, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant asserts that the prior art does not teach nor suggest all three component of the composition used in accordance with the method of the invention, namely (i) an antigen attached to (ii) an antibody that specifically binds to a molecule which is expressed by an antigen-presenting cell and (iii) an anti-CD40 antibody.

These assertions are inconsistent with applicant's acknowledgement that Anand et al. teach the use of antibody conjugates comprising antibodies that bind antigen presenting cells, including dendritic cells to deliver antigens in order to generate immunogenic compositions to a variety of antigens that Heath teaches the co-administration of a CD40 stimulating moiety as an adjuvant in combination with an antigen.
Therefore, the prior art teaching does include all three components of the composition used in the accordance with the method of the invention.

While applicant asserts that Heath does not teach nor suggest that the co-entrapment on/in a carrier system is an antibody that specifically binds to a molecule which is expressed by an antigen presenting cells, applicant also has acknowledged that combining antigen and/or adjuvant to increase the association between antigen and CD40 binding moiety.

Applicant argues that Heath does not teach that the antigen is attached to an antibody that targets the antigen to an antigen-presenting cell and that Anand et al. does not teach the use of anti-CD40 antibody.

One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

Applicant asserts that one of ordinary skill in the art would not have had a reasonable expectation of producing a synergistic enhancement or suppression of at least the humoral immune response or CD4 Th1 immune response to a target antigen by combining the teaching so the cited references.

A statement or argument by the attorney is not factual evidence.

Applicant has not provided objective evidence to support the assertion that the prior art teachings supporting the combination of antibody-antigen conjugates in combination with the adjuvant anti-CD40 would not result in immune responses greater than each element alone. Adjuvants are substances that enhance or potentiate the immune response to an antigen. Clearly, the administration of anti-CD40 antibody alone would not enhance or potentiate an immune response to an antigen. In addition, Heath teach that CD40 stimulators can enhance antibody responses to pneumoccocal polysaccharides in individuals unable to respond to polysaccharide only based vaccines (see Example 5, including paragraph 0126.

Therefore, the prior art does provide an expectation of success in producing an immune response greater than the simple sum of antibody-antigen conjugates and anti-CD40 antibodies acting alone.

Also, as pointed out above; page 36, paragraph 2 of the instant specification further discloses that "if we are to consistently take advantage of the adjuvant or immunosuppressant properties of CD40 ligation, the dynamics of antigen targeting so as to interpose CD40 at the optimal moment or location will need to be determined for the particular antigen system. In this regard, effective manipulation of APC surface molecules in vivo may not be possible".

Therefore, it is not clear that applicant's reliance on synergistic results is consistent with the disclosed Examples and disclosure that "effective manipulation of APC surface molecules in vivo may not be possible" with any antibody-antigen conjugate with anti-CD40 antibodies.

In contrast to applicant's assertions concerning that the prior art does not meet the elements of the claims the following of record is reiterated for applicant's convenience.

Anand et al. teach the use of antibody conjugates comprising antibodies that bind antigen presenting cells, including dendritic cells (e.g. column 2, paragraphs 4 and 6), to deliver antigens in order to generate immunogenic compositions to a variety of antigens (e.g. column 7, paragraph 2) (see entire document, including Summary of the Invention and General Description of the Invention). Anand et al. Teach that these is applicable to any antigen which it is desired to target to antigen presenting cells, including antigens derived from viruses, bacteria and tumors (see column 7, paragraph 1)

Heath teaches the co-administration of a CD40 stimulating moiety (e.g. anti-CD40 antibodies) (e.g., see paragraphs 0055, 0061, 0062) and the appropriate antigen, including the use of covalent linkage or co-entrapment as a vaccine (e.g. see paragraphs 0026-0027 and 0029) to a variety of antigens (see entire document, including Summary of the Invention).

In addition to the variety of antigens as well as the general applicability of antigens as taught by Anand et al. and Heath, applicant's election, filed 11/3/03, notes that the ordinary artisan would reasonably expect that results obtained by the invention with experimental antigens such as hen egg lysozyme and avidin are also predictive of results expected with the invention with regard to antigens associated with any of a large number of pathologies. Given applicant's admission that the specific class and type of antigen are obvious variants over one another, the species of classes and types of antigens are held obvious in view of one another in the instant application.

Although Anand is silent about aged or immuno-compromised individuals, the ordinary artisan would have immediately envisaged or would have found it obvious to activate the immune response is such individuals, given the prior art teachings of stimulating immune response to a variety of antigens, including pathogens and tumor associated antigens (e.g. see column 7, paragraph 2 of Anand et al.). Also, it is noted that Anand et al. teach that the quantity to be administered depends on the subject to be treated, including the capacity of the individual's immune-system to synthesize antibodies and to produce a cell-mediated immune response (column 9, paragraph 1).

In addition, Heath teaches that providing anti-CD40 with antigen has an advantage for the vaccination of patient with immune deficiencies (paragraph 0126).

Therefore, it would have obvious for the ordinary artisan to enhance immune responses or vaccinate aged or immunocompromised individuals as well as subjects fifty years or older in order to stimulate immune responses or to vaccinate such individuals to a wide variety of antigens based on need. For example, boosting immune responses to a variety of antigens (e.g. pathogens or tumor antigens) in such individuals was known and practiced at the time the invention was made.

Given the teachings of Heath to provide anti-CD40 with antigen in composition form or as a conjugate (see Summary of the Invention) and the teachings of Anand et al. to provide antigen with anti-antigen presenting cell / dendritic cell antibodies; it would have been obvious to one of ordinary skill in the art to administer the antigen in the context of such antigen-antibody conjugate with the immunostimulatory anti-CD40 antibodies to boost the immune response to a wide variety of desired antigens, including providing both components in the same composition, as taught by Heath (see paragraphs 0026-0027 and 0029).

In addition, the motivation to combine the prior art can arise from the expectation that the prior art elements will perform their expected function to achieve their expected results when combined for their common known purpose. Here, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine both antigen-antibody conjugates for dendritic cells and CD40-specific antibodies to target antigens to the antigen presenting cells of interest, including CD40-expressing antigen presenting cells, as well as to enhance the immunogenicity of said antigens.

Given the teachings of Anand et al. and Heath; the ordinary artisan would have been motivated to target professional antigen presenting cells such as dendritic cells with the combination of antigen-antibody targets and the immunostimulatory agonistic CD40 antibodies to enhance the immune response to a wide variety of antigens. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

9. No claim allowed.

10 Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
August 4, 2004